To the editor:

Risk of second cancers in chronic myeloproliferative neoplasms

We read with interest the article by Frederiksen et al about the increased risk of developing hematologic and nonhematologic cancers in a large cohort of Danish patients with myeloproliferative neoplasms (MPNs).[1] In a previous study[2] we reported that MPN patients have a 3.44-fold higher risk of lymphoid neoplasms compared with the general population, in line with current[1] and other results.[3] Considering nonhematologic cancers, Frederiksen et al reported a standardized incidence ratio (SIR) value of 1.2 (95% CI: 1.0-1.4) for essential thrombocythemia (ET) and 1.4 (95% CI: 1.3-1.5) for polycythemia vera (PV).[1] These estimates were based on 1578 ET and 4625 PV patients after a median follow-up of 4.0 and 5.0 years, respectively.

We have followed a series of 733 MPN patients, 302 PV, 375 ET, and 56 primary myelofibrosis, consecutively diagnosed at the Hematology Section, University of Florence, from 1980 to 2006, all under an active clinical follow-up protocol and residing in a defined area of Tuscany, central Italy. The identification of cancer cases was obtained through individual chart records and linkages with the hospital discharge system, pathology department registries, Regional Cancer Registry, local town offices, and Regional Mortality Registry. For each subject, the period at risk started from the date of MPN diagnosis to the date of diagnosis of subsequent primary cancer, death, or December 31, 2006 (end of follow-up), whichever came first. The mean follow-up period was 6.45 years with a total of 4724.72 person-years. The specific cancer incidence rates in the general population were provided by the Tuscany Cancer Registry, which is active in the same area since 1984 and involves 1 161 000 inhabitants; SIRs were calculated as the ratio of observed to expected cases. The study was conducted in accordance with institutional guidelines after approval by local ethics committee.

Results showed the absence of a specific pattern of risk of cancer of all sites (SIR = 0.87, 95% CI: 0.64, 1.14) except for melanoma cases for which we found a significantly elevated risk compared with the

Table 1. Nonhematologic cancer incidence in 733 MPN patients, overall and by specific site*; number of observed and expected cases, relative risks as estimated by standardized incidence ratios (SIR) and 95% confidence intervals (1980-2006 period).

Any MPN	Cancer site	ICD IX	Observed†	Expected‡	SIR§	95% CI
	Digestive system	150-159	10	15.08	0.63	0.33-1.16
	Stomach	151	4	3.41	1.11	0.42-2.85
	Colon & Rectum	153-154	5	7.75	0.61	0.25-1.46
	Respiratory system	160-165	7	7.73	0.86	0.41-1.80
	Lung	162	6	6.68	0.85	0.38-1.90
	Melanoma	172	4	1.03	3.69	1.39-9.64
	Skin (non-melanoma)	173	9	9.06	1.03	0.56-1.92
	Breast	174	5	5.96	0.79	0.33-1.90
	Prostate	185	4	5.56	0.68	0.25-1.80
	Bladder	188	3	2.46	1.15	0.37-3.58
	Kidney and other urinary organs	189	2	1.67	1.12	0.28-4.48
	All cancer sites‖	140-199	49	56.62	0.87	0.64-1.14
PV	**Cancer site**	**ICD IX**	**Observed†**	**Expected‡**	**SIR§**	**95% CI**
	Digestive system	150-159	6	7.26	0.83	0.37-1.84
	Colon & Rectum	153-154	4	3.70	1.08	0.41-2.88
	Respiratory system	160-165	3	4.23	0.71	0.23-2.20
	Lung	162	3	3.63	0.83	0.27-2.56
	Melanoma	172	2	0.47	4.26	1.06-17.04
	Skin (non-melanoma)	173	6	4.33	1.38	0.62-3.08
	Prostate	185	2	3.18	0.63	0.16-2.52
	Bladder	188	3	1.33	2.25	0.73-6.98
	Kidney and other urinary organs	189	2	0.68	2.96	0.74-11.84
	All cancer sites‖	140-199	26	26.98	0.96	0.63-1.41
ET	**Cancer site**	**ICD IX**	**Observed†**	**Expected‡**	**SIR§**	**95% CI**
	Digestive system	150-159	3	6.90	0.43	0.14-1.35
	Stomach	151	2	1.53	1.30	0.33-5.23
	Respiratory system	160-165	4	2.91	1.37	0.52-3.66
	Lung	162	3	2.54	1.18	0.38-3.67
	Skin (non-melanoma)	173	3	4.14	0.72	0.23-2.25
	Breast	174	5	3.95	1.26	0.52-3.04
	Prostate	185	2	1.85	1.08	0.27-4.33
	All cancer sites‖	140-199	22	26.22	0.84	0.53-1.27

*Only cancer sites with at least 2 observed cases.
†Cases of cancer newly diagnosed in MPN patients.
‡Expected cases of cancer according to incidence rates in the general population of the area applied to the number of person years in the study follow up.
§Standardized incidence ratio, obtained from the ratio of Observed to Expected cases ‖ except lymphoproliferative neoplasm

general population (SIR = 3.69, 95% CI: 1.39, 9.64; Table 1); however, because of the low number of cases (2 PV, 1 ET, and 1 myelofibrosis) such an association remains to be validated. The analyses stratified by sex (361 males/372 females), *JAK2*V617F mutational status (340 *JAK2*V617F mutated/137 wild-type), and cytotoxic therapy with hydroxyurea (59.6% of 659 evaluated) did not show any specific risk pattern (not shown in detail).

Our study is based on a smaller population compared with Frederiksen et al[1] and has the advantages of a slightly longer follow-up and of being conducted in a narrower area with an active local registry. Our carefully controlled patient series reduces the risk of possible misclassification at baseline, potentially present in a very large series obtained in a country-wide study, as mentioned by the authors.[1] In any case, we believe that the low SIR value (1.2 to 1.4) found in the Danish study,[1] together with our negative results, should call for much caution before accepting d'emblée the idea that the incidence of nonhematologic cancers is specifically increased in MPNs and, even more, before discussing such topic with the patients.

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Response

Cancer risk in chronic myeloproliferative neoplasms

We thank Susini and colleagues for their comments[1] to our article on the risk of a new cancer in patients with chronic myeloproliferative neoplasms (CMPNs).[2] We have read the results from their CMPN cohort from Tuscany with interest. We agree that any novel finding must be confirmed before generally accepted and shared with patients. However, other studies have found results in line with ours. Fallah et al reported an increased risk of kidney cancer, melanoma and nonmelanoma skin cancer, as well as endocrine cancers among patients diagnosed with polycythemia vera (PV).[3] Nielsen et al reported an increased risk of any cancer among *JAK2* V617F mutation-positive persons from the general population.[4] In their study most new malignancies were CMPNs but also solid tumors were reported.[4] Although we cannot rule out an effect of diagnostic misclassification of CMPNs in our study it is reassuring that we found similar risk of a new cancer among patients with chronic myeloid leukemia (CML) among whom diagnostic misclassification seems unlikely. We also found the expected increased risks of new hematologic malignancies. Furthermore, our results were robust across stratification according to a previous or current diagnosis of chronic obstructive pulmonary disease. The excess risk of nonhematologic cancers in our study is modest, ranging from 1.2 to 1.6, and might only be detectable in larger studies.

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